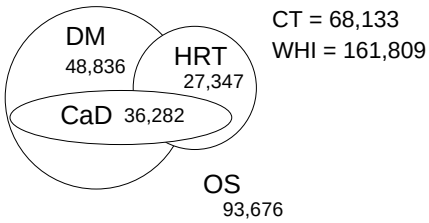
Trial Implementation I:
Recruitment, Retention and Adherence

Andrea Z. LaCroix, PhD
Fred Hutchinson Cancer Research Center
Professor of Epidemiology
University of Washington

Design of WHI

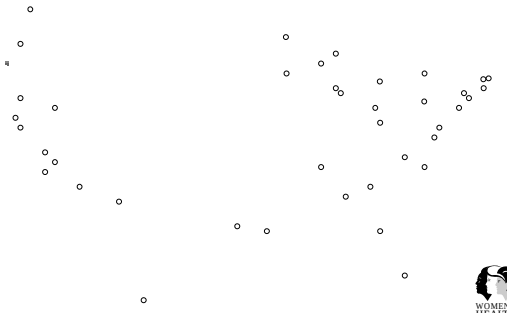


CT = 68,133
WHI = 161,809

WHI Clinical Centers

- 40 Centers in urban, suburban and rural areas
- 10 minority centers with access to American Indian, African American, Asian American/Pacific Islander, and Hispanic populations (expected to have 60% minority participants)

Women's Health Initiative Clinical Centers



WHI Hormone Program
Study Population: Inclusion criteria

- Age 50-79 at baseline
- Post menopausal, defined as:
  - No bleeding for >6 months (>12 months for 50-54 years old)
  - Current / prior use of menopausal hormones
  - Post hysterectomy with symptoms
- Likely to reside in the clinic area for 3 years
- Willing to provide written informed consent

Exclusion criteria

- Adherence
  - Poor compliance to placebo run-in, unwilling to discontinue hormone therapy, behavioral issues
- Competing risk
  - Expected survival < 3 years, prior breast or endometrial cancer
- Safety
  - Bleeding disorders, low hematocrit

Study Population: Exclusions for Adherence reasons

- Severe menopausal symptoms that would make placebo intolerable
- Unable or unwilling to discontinue use of HRT
- Inadequate adherence to placebo run-in
- Substance abuse (alcoholism, drug dependency)
- Mental illness or dementia
- Active participant in another intervention trial
- Unable or unwilling to discontinue oral or injectable testosterone
- Unwilling to have a baseline or follow-up endometrial aspiration

Study Population: Competing risk exclusions

- Any medical condition likely to be associated with a predicted survival of $\leq$ 3 years
- Invasive cancer in last 10 years (except nonmelanoma skin cancer)
- Prior breast cancer (in situ or invasive)
- Mammogram or clinical breast exam suspicious of malignancy
- History of acute MI, stroke or TIA in the last 6 months
- Known chronic active hepatitis or severe cirrhosis

Study Population: Safety exclusions

- Severely underweight (recommended lower limit of 18 kg/m^2)
- Hematocrit < 32%; Platelets < 75,000 cells/ml
- Lipemic serum leading to a diagnosis of hypertriglyceridemia
- History of bleeding disorder serious enough to require transfusion
- Severe hypertension (>200/105)
- History of pulmonary embolism or deep vein thrombosis (traumatic added as a criterion in 1997)

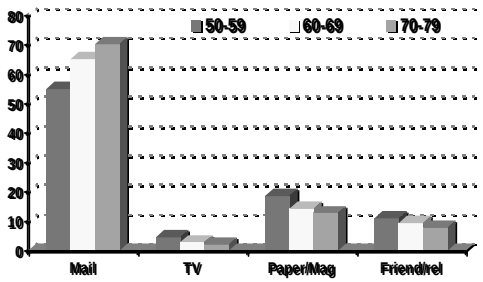
Study Population: Safety exclusions (continued)

- Current use of oral corticosteroids, anticoagulants, tamoxifen, SERMS
- Prior endometrial cancer; Endometrial hyperplasia at baseline
- Malignant melanoma at any time

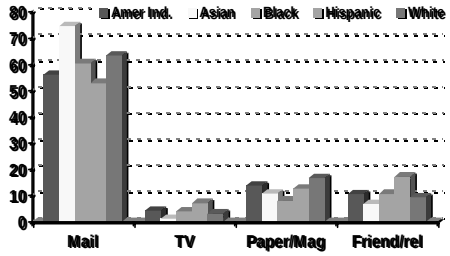
WHI Initial Screening

- Mass mailing of recruitment brochure
  - provided basic information about WHI
  - postage-paid return postcard to indicate interest
- Telephone screening by trained interviewers
- Clinic visits
  - 3-5 for enrollment in the Clinical Trial
  - 1 for enrollment in the Observational Study

Type of Initial Contact with WHI



Type of Initial Contact with WHI



WHI Recruitment Materials

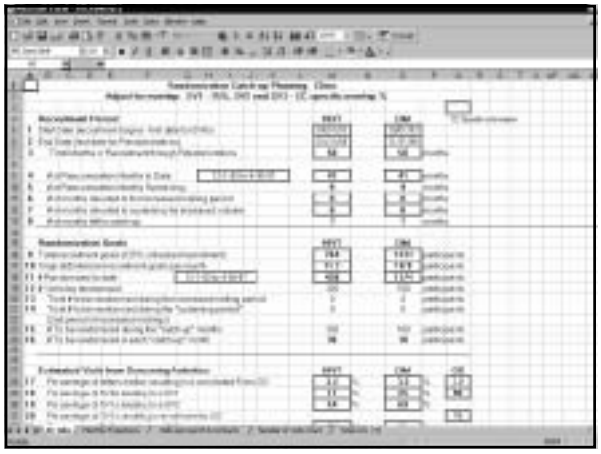
- Brochures for mass mailing
- Videos
  - Recruitment
  - Consent
  - Retention
- Tell-a-friend postcards
- Posters and flyers
- Public Service Announcements for radio, TV, and print media
- WHI Logo magnets, buttons, stickers

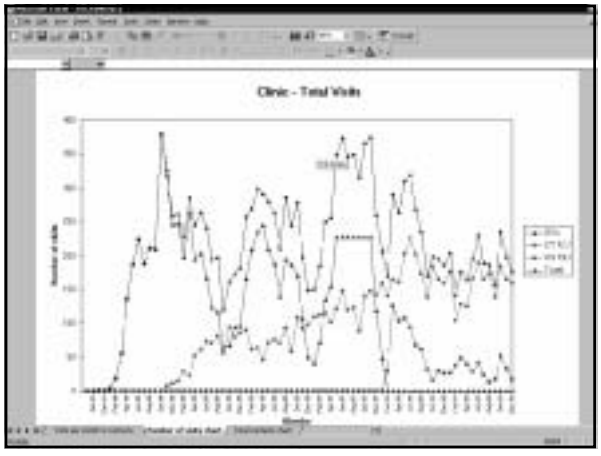
WHI Recruitment: National Activities

- Recruitment goal monitoring
- Study progress reports
- Development of materials and procedures
- Conducted a public relations campaign
- Provided ongoing daily support to clinic recruitment staff
- Provided a national toll free phone number automatically linking women to their local clinic

WHI Recruitment: Local Clinic Activities

- Recruitment coordinators designated to lead effort
- Mass mailings-1000-5000 brochures/month
- Mailing rates adjusted based on local return rates
- Local tracking systems varied widely
- Mailing lists came from multiple sources
  - motor vehicle registration lists
  - voters' registration lists
  - drivers' license lists
  - HMO enrollees
  - HCFA
  - commercial/targeted mailing lists





WHI Recruitment: Creative Local Strategies

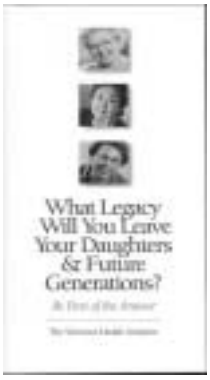
- Airplane message flying over OSU football game
- Local and national celebrities including Ms. Senior America, Olympia Dukakis
- Collaboration with local businesses to fund incentive items, newsletters, and transportation
- Planned events such as fashion shows
- Paid advertisements on buses, billboards, coupon packs, employee payroll stuffers

WHI Recruitment: Special Accommodations to Encourage a Diverse Population

- Allowing extra time at screening visits for older women
- Providing extra assistance for women with physical limitations
- Using large size print, good color contrasts
- 6th grade reading level
- Spanish translation

WHI "Branding"

- All materials printed with WHI logo
- WHI colors
- Consistent use of visual images (three heads logo)
- And verbal messages: "Be part of the answer," passing on a legacy of good health



Recruitment materials were translated into Spanish.

Postcards were developed for recruited women to mail to their friends and family.

A special letter signed by the NIH Director of WHI was developed to entice older women to participate.

Public Service Announcements appealed to women's sense of altruism and desire to better the health of their daughters and families.

Special Public Service Announcements were developed to appeal to minority women.

A national campaign was developed featuring Angela Lansbury with radio and print media materials.


HEALTH NEWS

Study of Women's Health Issues Focuses on Disease Prevention

WOMEN'S HEALTH INITIATIVE

Newspaper articles were developed to encourage women to enroll.

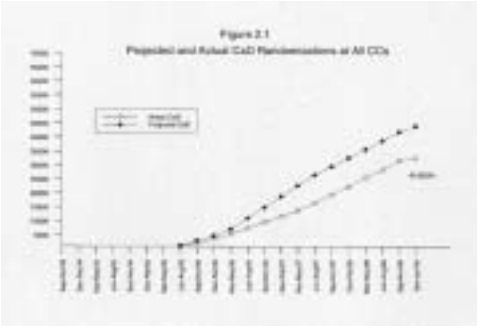
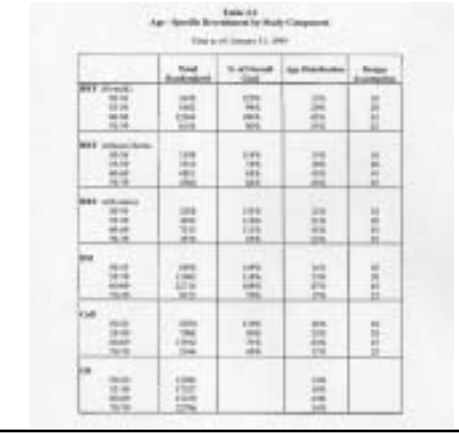


Figure 2.1

Projected and Actual CaD Randomizations at All CCs



Baseline Characteristics of WHI Final Enrollment Participants

	PHT N=27,347		DM N=48,836		CaD N=36,282		OS N=93,676	
	N	%	N	%	N	%	N	%
Age at Screening								
50 – 54	**3425**	**12.5**	**6958**	**14.2**	**5157**	**14.2**	**12386**	**13.2**
55 – 59	**5402**	**19.8**	**11041**	**22.6**	**8264**	**22.8**	**17319**	**18.5**
60 – 69	**12364**	**45.2**	**22714**	**46.5**	**16521**	**45.5**	**41197**	**44.0**
70 – 79	**6156**	**22.5**	**8123**	**16.6**	**6340**	**17.5**	**22774**	**24.3**

Baseline Characteristics of WHI Final Enrollment Participants

	PHT N=27,347		DM N=48,836		CaD N=36,282		OS N=93,676	
	N	%	N	%	N	%	N	%
Race / Ethnicity								
American Indian	131	0.5	203	0.4	149	0.4	422	0.5
Asian / Pacific Islander	527	1.9	1107	2.3	722	2.0	2671	2.9
Black	2741	10.0	5266	10.8	3317	9.1	7639	8.2
Hispanic	1543	5.6	1854	3.8	1507	4.2	3623	3.9
White	22027	80.5	39760	81.4	30153	83.1	78013	83.3

Baseline Characteristics of WHI Final Enrollment Participants

	PHT N=27,347		DM N=48,836		CaD N=36,282		OS N=93,676	
	N	%	N	%	N	%	N	%
Body-mass Index, kg/m²								
Underweight *(<18.5)*	**157**	**0.6**	**154**	**0.3**	**148**	**0.4**	**1107**	**1.2**
Normal *(18.5 – 24.9)*	**7107**	**26.1**	**12503**	**25.7**	**9430**	**26.1**	**36687**	**39.6**
Overweight *(25.0 – 29.9)*	**9533**	**35.1**	**17387**	**35.8**	**12955**	**35.9**	**31463**	**34.0**
Obesity I *(30.0 – 34.9)*	**6183**	**22.7**	**11198**	**23.0**	**8203**	**22.7**	**14578**	**15.8**
Obesity II *(35.0 – 39.9)*	**2807**	**10.3**	**5048**	**10.4**	**3644**	**10.1**	**5451**	**5.9**
Extreme Obesity *(>40)*	**1405**	**5.2**	**2322**	**4.8**	**1715**	**4.8**	**3282**	**3.6**

WHI Adherence

Definition:

- The degree to which the women follow the recommended behavior, *as prescribed.*
  - What percentage of their pills do they take?
  - To what degree do they follow the prescribed dietary recommendations?

Retention

Definition:

- Whether women remain as participants, at some definable level, in the study
  - Are they available for follow-up assessments?
  - Do they come to visits?
  - Do they complete forms?
  - Most importantly, are they providing ***outcome*** information?

WHI Adherence and Retention Efforts: A Brief History

- Development and refinement of manuals
- Formation of the Performance Monitoring Committee
- Development of monitoring reports at the study, clinic and individual participants levels
- HRT Summit (Winter, 1997)
- Adherence and retention compendium (Hot Tips; Fall 1997-Winter 1998)
- Dietary Modification Trial Summit (Winter, 1998)
- Adherence and retention workshops (Spring, 1998)

Retention and Adherence Prevention Strategies

Primary Prevention:

– Strategies to minimize the number of participants enrolled who are potential risks for poor retention and adherence

– Strategies to keep participants “on track”

Source: Sally Shumaker, Adherence and Retention Workshop, May, 1998

Retention and Adherence Prevention Strategies

Secondary Prevention:

– Early identification and tracking of participants whose adherence is “slipping”

– Strategies to assist participants to improve adherence/retention

Tertiary Prevention:

– Restarting intervention, re-gaining drop-outs

Retention and Adherence Primary Prevention

Step 1: Identify the most promising participants

Problem: Striving towards recruitment goals must be balanced against the need to recruit participants who are fully committed to the study.

Retention and Adherence Primary Prevention

During screening:

- Fully inform participants about study burden, do not minimize inconvenience and effort required
- Fully inform that benefits may not accrue to the participant in a research trial
- Fully inform about the meaning of randomization
- Inquire about their past intervention behavior
- Employ a “run-in”
- Attend to subtle and overt cues during screening visits (rescheduling, lateness, difficulty contacting, hesitancy, etc.)

Retention and Adherence Primary Prevention

Step 2: Keeping enrolled participants “on track”

- Track behavior and performance carefully
- Clear communication channels among staff
- Early identification of “at risk” participants
- Rewards/recognition/reinforcement for good adherence
- Incentives for participants’ involvement in the study

Retention and Adherence Multi-tiered Approaches

CCC Liaison

- communicates directly with clinics
- offers technical assistance
- conducts retention conference calls
- runs an e-mail retention support group

Performance Monitoring Committee

- reviews clinics, provides recommendations

A&R Working Group

- addresses global, study-wide issues and strategies

Retention and Adherence
National Retention Efforts

- Annual incentives (small gifts)
- *WHI Matters* newsletter
- Thank you/retention letters from NIH
- Close-out materials to recognize participation

Participant ID cards were issued to increase awareness of being part of the study and "part of the answer" as well as promote proactive mailing of medical records.

Certificates of recognition were given to women for their continued participation over time.

WHI Matters **Newsletter is published 2-3 times yearly.**

- **Mailed and posted on the WHI participant website**
- **Contains articles on health topics, profiles on WHI participants, Resources and FAQs.**
- **Does *not* discuss intervention topics.**

A separate newsletter was developed for participants in the intervention arm of the Dietary Modification Trial. This newsletter could reinforce the dietary intervention.

Clinic Staff Support

- **Provide training**
  - Use of data resources
  - Behavioral strategies (motivational interviewing)
  - Good interviewing and listening skills
- **Provide staff TLC (incentives, retreats, sensitivity to burn-out, stress management)**
- **Form a multidisciplinary clinic A&R Committee**

Clinic Automated Retention Forms

- ***Form 24*** *- Adherence and Retention Worksheet*
- ***Form 23*** *- Search to Locate Participant*
- ***Form 7*** *- Participation Status*
- *Participants with Undeliverable Addresses*
- *Participants with Incomplete or wrong Name/Address*
- *Participant Transfer Form*

Clinic Automated Adherence and Clinical Management Reports

- HRT and/or CaD Bottles overdue for collection
- Participants needing HRT or CaD dispensation
- Task Completeness
- Missing lab results
- Mammogram due
- HRT/CaD medication adherence
- Safety events
- HRT/CaD management recontact

Adherence Activities in the Dietary Modification Trial

2000 Intensive Intervention Program

– 3 interviews using motivational enhancement counseling techniques

2001 Targeted Message Campaign

– mailing designed to help women rediscover their intrinsic motivation for participating in WHI

– followed by a supportive motivational enhancement call

Adherence Activities in the Dietary Modification Trial

2002 Personalized Evaluation of Fat Intake

– tailored, food-based, feedback to facilitate dietary goal re-setting for participants

– identified top 5 sources of fat from foods for each participant

– nuts, popcorn made with oil, meat, peanut butter, cheese

Adherence Activities in the Dietary Modification Trial

2002 Lead nutritionist workshop
- behavioral booster training
- re-energizing by sharing information
- identifying local options to support pt. Adherence

2003 Centralized Personalized Evaluation of Food Intake

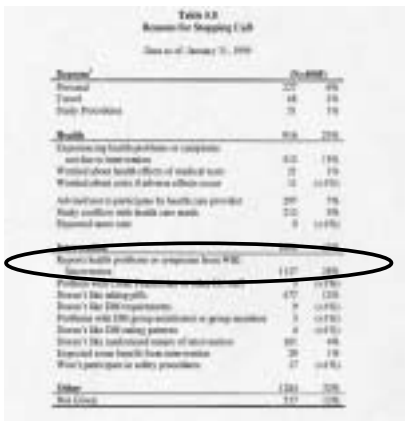
2003-4 CCC is leading a series of dietary behavioral-focused conference calls with clinic nutritionists

Improving Adherence in the CaD A Case Example

Early CaD Adherence was low (~60% had >80% adherence).

CCC performed survival analyses with time to first non-adherent visit as the outcome. Factors predicting poor adherence were:
- younger age
- minority ethnicity
- unmarried status
- not having a 4-week adherence phone contact
- moderate to severe symptoms of gas or constipation

Women who stopped CaD reported problems taking the pills.



Improving Adherence in the CaD A Case Example

- **Increased awareness of problems with chewable formulation:**
  - taste
  - consistency
  - size
  - hardness
- **Survey of 100 CaD ppts at 4 volunteer CCs**
  - confirmed that formulation was a problem for ppts
  - physical symptoms were less problematic

CaD Innovations

- Taste test (7/96)
- Participant material revisions (9/96)
- 4-week call (10/96)
- CaD survey of 100 participants (late 1996)
- New swallowable formulation (10/97)
- Swallowable re-formulation (early 1998)

Hot Tips: CaD Recruitment

- Maintain enthusiasm for CaD
  - with staff and participants
  - during screening and follow-up
- Emphasize the science
  - tie into local incidence rates
- Spend extra time with participant
  - during informed consent process
  - answering questions (see "*Q&A*")
  - emphasizing commitment, don't have to stop supplements, potential side effects
- Provide a visual inspection and offer a taste test

Hot Tips: Adherence

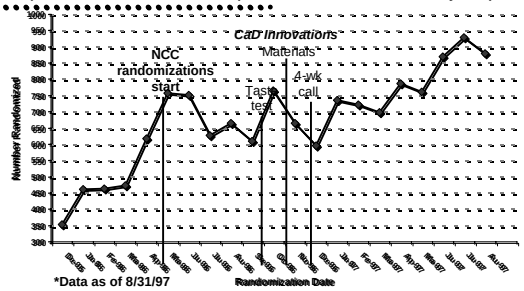
- Screen for good adherers during recruitment
- Conduct the 4-week call
  - in window
  - using consistent staff
- Develop a structure to support adherence
  - designate a key retention staff person
  - have monthly retention committee meetings
  - identify candidates for and implement IAP
  - make appropriate referrals

Hot Tips: Adherence

- Support adherence during ppt interactions
  - continue to stress the importance of the trial
  - be responsive, attentive, and supportive to ppts
  - offer a 2nd or larger pill organizer
  - offer step-downs and step-ups, “pill holidays”
  - offer new formulation
- Emphasize the need to return/track bottles
  - get estimates if bottle is not returned
  - provide mailers
  - provide medication bags/totes at follow-up contacts

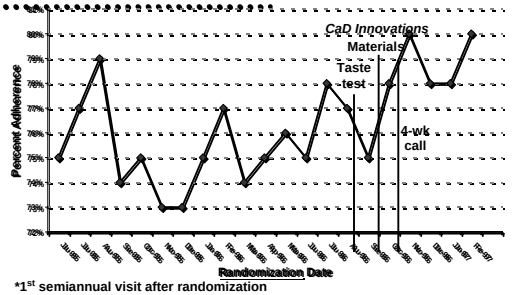
CaD Randomizations each Month

(VCC and NCC combined: Participants randomized at AV1 after May 1995)*

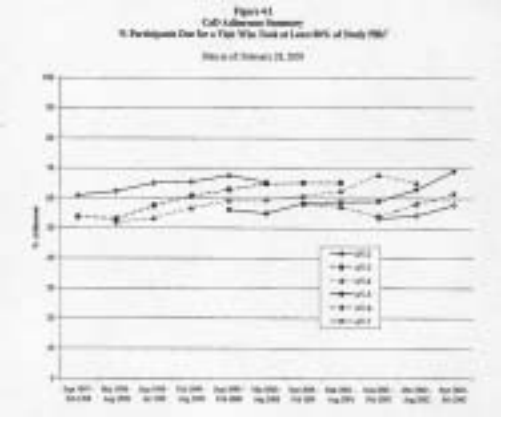


CaD Adherence at Semi Annual Visit 2*

(VCC and NCC combined: Participants randomized at AV1 after May 1995 and due for SA2)**



*1st semiannual visit after randomization
**Data as of 8/31/97; N=173-573



Conclusions: Recruitment

1. Retention begins at recruitment, *really*.
2. WHI was privileged to have a national recruitment infrastructure and $1 million to spend on national recruitment efforts.
3. Mass mailing was the backbone of our recruitment success.
4. Minority recruitment was a challenge, but tenacious effort paid off.

Conclusions: Retention and Adherence

1. The greatest success comes from systematized *pro-active* efforts and individualized *reactive* efforts.
2. Adherence monitoring and special studies can help to inform innovations that improve adherence.
3. Encouraging clinic staff (e.g. nurses) to become more data savvy is an important future direction.